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EXAMINER	
MYERS, CARLA J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,550	WILDENBERG ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-31 and 33* is/are pending in the application.

4a) Of the above claim(s) *30,31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the reply filed on July 10, 2009. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance.

All rejections not reiterated herein are hereby withdrawn.

In particular, the rejection of claims 18-29 under 35 U.S.C. 112, first paragraph (new matter) has been obviated by the amendments to the claims. The provisional rejection of claims 18-29 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/631,714 in view of Singh et al has been obviated by the cancellation of claims 1-17 in the '714 application.

This action contains new grounds of rejection necessitated by these amendments to the claims and is made Final.

2. Claims 18-31 and 33 are pending.

Claims 18-29 have been examined herein.

Claims 30, 31 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on February 16, 2007.

Maintained Rejections

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-29 are indefinite over the recitation of "said aneuploidy being determined by an unequal binding." This phrase is not clearly defined in the specification or claims and there is no art recognized definition for this phrase as it relates to determining aneuploidy. It is unclear, for example, as to whether unequal binding refers to a difference in the quantity of sample polynucleotide hybridized to binding agents as compared to standard polynucleotides hybridized to binding agents, as determined by a difference in the quantity of signal emitted by hybrids formed by the fluorescently-labeled polynucleotide samples to the binding agents as compared to the fluorescently-labeled polynucleotide standards to the binding agents, or whether unequal binding refers to the specificity of hybridization or the degree to which two sequences that are not fully complementary to one another bind.

Claims 27-29 are indefinite over the recitation of "said binding agent comprises a nucleic acid immobilized on a microparticle" (claim 27, lines 1-2) because it is not clear as to how this recitation is intended to further limit the claims from claim 18. Claim 18 requires that the binding agent comprises a polynucleotide immobilized onto microparticles. It is thereby unclear as to whether the binding agent comprises both the polynucleotide and the nucleic acid, or whether the nucleic acid is intended to be the same as the polynucleotide, and/or whether the microparticle attached to the nucleic

acid is the same as or distinct from the microparticle attached to the polynucleotide. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Response to Remarks:

In the response, Applicant's state that the rejections have been overcome by the amendment to the claims. However, the amendments did not address the above grounds of rejection. The rejections are maintained for the reasons stated above.

New Grounds of Rejection:

Claims 18-29 are indefinite over the recitation of "binding of said sample and said sample to said binding agent" (see claim 18, step (vi)). It is unclear as to whether this phrase is intended to refer to the binding of the sample to the sample, or the binding of the sample to the sample and to the binding agent, or only to the binding of the sample and the binding agent. It appears that the claims intend to refer to "binding of said sample and said standard to said binding agent."

4. The following grounds of rejection were presented in the Office action of March 10, 2009. The rejections have been modified herein to address the amendments to the claims. In particular, it is noted that the claims have been amended to delete the recitation of "mixing non-equal amounts of said sample and said standard." The claims have also been amended to recite a method for detecting aneuploidy in a subject, rather than "aneuploidy in one or more chromosomes."

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).ok

Claims 18-21, 23, 24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel (U.S. Patent No. 6,562,565) in view of Mohammed (PGPUB 2003/0124584), and further in view of Singh et al (WO 02/40698; cited in the IDS of 11/2/06).

Pinkel (col. 2, lines 30-43; col. 3, lines 15-42) teaches a method of determining the copy number of chromosomal sequences (i.e., a method of detecting aneuploidy) comprising the steps of producing fluorescently-labeled test/sample nucleic acids from a subject (col. 3, lines 15-42, col. 10, lines 41-67); producing fluorescently-labeled polynucleotide reference/standard nucleic acids from a normal sample containing two copies of each autosomal sequence and having one or two copies of each sex chromosomal sequence depending on gender (i.e., non-aneuploid fluorescently-labeled polynucleotide standards) wherein the test/sample nucleic acids and the

reference/standard nucleic acids are labeled with fluorophores having different emission spectra (col. 3, lines 22-27 and col. 10, lines 41-67); mixing equal quantities of the test/sample nucleic acids and the reference/standard nucleic acids (col. 12, lines 28-38, col. 13, lines 41-50) with a limiting amount of "target nucleic acids" (i.e., nucleic acid binding agents) immobilized onto solid supports that are labeled with a fluorescent moiety; detecting the amount of binding between the test/sample nucleic acids and the binding agents and the amount of binding between the reference/standard nucleic acids and the binding agents, and comparing the amounts of binding wherein an increase in binding of the test/sample nucleic acids as compared to the reference/standard nucleic acids indicates an increase in copy number and a decrease in the binding of the test/sample nucleic acids as compared to the reference/standard nucleic acids indicates a decrease in copy number (i.e., wherein an unequal binding indicates aneuploidy; column 2, lines 66-67 and column 3, lines 1-6).

In particular, Pinkel teaches that the nucleic acid binding agents may be on separate supports, such as a plurality of beads (column 2, lines 55-56), and that the target elements are typically from 1μM to 3mM (i.e. microparticles, column 4, lines 26-31 and col. 8, lines 59-61). Pinkel also teaches that beads of various sizes can be used (column 8, lines 57-61). Accordingly, Pinkel teaches that the nucleic acid binding agents are immobilized onto microparticles of distinct sizes.

Regarding the recitation in the present claims that the sample and standard nucleic acids are mixed with a limiting amount of binding agents, Pinkel teaches that “Small array members containing small amounts of concentrated target DNA are

conveniently used for high complexity comparative hybridizations since the total amount of probe available for binding to each element will be limited. Thus, it is advantageous to have small array members that contain a small amount of concentrated target DNA so that the signal that is obtained is highly localized and bright" (col. 8, line 61 to col. 9, line 1). Accordingly, Pinkel teaches that small amounts of the target nucleic acid/binding agent are present so that limiting amounts of the target/binding agent are available for binding to the sample and reference nucleic acids. It is noted that the term “limiting” is not defined in the specification or claims and thereby the disclosure of Pinkel of using small amounts of target nucleic acid /binding agent meets the limitation in the claims of a “limiting amount” of binding agent.

Further, Mohammed clarifies that the CGH method, as taught by Pinkel, is a method of competitive binding.

Specifically, Mohammed (para [0004]) teaches that:

“The principle of the array CGH approach is simple. Equitable amounts of total genomic DNA from cells of a test sample and a reference sample (e.g., a sample from cells known to be free of chromosomal aberrations) are differentially labeled with fluorescent dyes and co-hybridized to the array of BACs, which contain the cloned genomic DNA fragments that collectively cover the cell's genome. The resulting co-hybridization produces a fluorescently labeled array, the coloration of which reflects the competitive hybridization of sequences in the test and reference genomic DNAs to the homologous sequences within the arrayed BACs” (emphasis added).

Accordingly, the ordinary artisan would have recognized that the method of Pinkel should be performed using limiting amounts of binding agents for each chromosome in order to achieve the objectives set forth by Pinkel and Mohammed of providing a competitive hybridization assay that allowed for the determination of the occurrence of a copy number change (aneuploidy) in the test sample.

Regarding the recitations of a competitive binding assay "for detecting aneuploidy," and "detecting aneuploidy by comparing the signal caused by the binding of said sample," it is noted that the present specification states that "aneuploidy is to be understood as any deviation from a euploid state in an organism, wherein euploidy is defined as a normal 2n set of chromosomes" (page 25). The specification goes on to recite that aneuploidy may also include "partial monosomy conditions wherein a part of a chromosome is deleted" (page 26). In view of this disclosure, the claims are considered to include methods which detect a change in copy number which is a deletion of a gene or a part of a chromosome. The method of Pinkel is considered to be one which detects "aneuploidy" as defined by the present specification. In particular, Pinkel states that "Variations in copy number detectable by the methods of the invention may arise in different ways. For example, copy number may be altered as a result of amplification or deletion of a chromosomal region. Alternatively, copy number may be reduced by genetic rearrangements that alter the sequences in the probe or target nucleic acids sufficient to reduce their binding" (col. 6, lines 55-63).

To any extent that the claims as amended are intended to be directed to a method which detect a "deviation from a euploid state in an organism" (i.e., an increase

or decrease in the total number of chromosomes), Pinkel does not specifically exemplify such methods. However, Pinkel does address the need to detect changes in the number of chromosomes, stating that "perinatal genetic problems frequently result from loss or gain of chromosome segments such as trisomy 21 or the micro deletion syndromes. Thus, methods of prenatal detection of such abnormalities can be helpful in early diagnosis of disease" (col. 1, lines 28-32).

Further, Mohammed teaches the application of the method of array-based CGH to the detection of a variation in the karyotype of a subject, and thereby to the detection of aneuploidy (para [0004], [0012]). Mohammed (para [0012]) teaches a method comprising:

an array-based comparative genomic hybridization (CGH), comprising the following steps: (a) providing an array comprising a plurality of cloned genomic nucleic acid segments, wherein each genomic nucleic acid segment is immobilized to a discrete and known spot on a substrate surface to form an array and the cloned genomic nucleic acid segments comprise a substantially complete first genome of a known karyotype; (b) providing a first sample, wherein the sample comprises a plurality of genomic nucleic acid segments comprising a substantially complete complement of the first genome labeled with a first detectable label; (c) providing a second sample, wherein the sample comprises a plurality of genomic nucleic acid labeled with a second detectable label, and the genomic nucleic acid sample comprises a substantially complete complement of genomic nucleic acid of a cell or a tissue sample, and the karyotype of the second sample is known and is different from that of the first sample of step (b); (d) providing a third sample, wherein the sample comprises a genomic nucleic acid sample with an unknown karyotype labeled with the second detectable label, and the genomic nucleic acid comprises a substantially complete complement of genomic nucleic acid of a cell or a tissue sample; (e) preparing serial dilution fractions of the samples of steps (c) and (d); (f) contacting the sample of step (b) separately with each serial dilution fraction of the sample of step (c) with the array of step (a) under conditions wherein the nucleic acid in the samples can specifically hybridize to the genomic nucleic acid segments immobilized on the array; (g) measuring the amount of first and second fluorescent label on each spot after the contacting of step (f) for each serial dilution fraction and determining the karyotype of each serial dilution fraction by comparative genomic hybridization; (h) contacting the sample of step (b) and serial dilution fractions of the sample of step (d) with the array of step (a) under conditions wherein the nucleic acid in

the samples can specifically hybridize to the genomic nucleic acid segments on the array; (i) measuring the amount of first and second fluorescent label on each spot after the contacting of step (h) for each serial dilution fraction and determining the karyotype of each serial dilution fraction by comparative genomic hybridization; and, (j) selecting which dilution fraction karyotype determination of step (g) most closely determined the known karyotype, and selecting the same serial dilution measurement in step (i) to determine the karyotype of the sample of step (d), thereby determining the degree of genetic mosaicism in a cell population.

Mohammed specifically teaches that the array-based CGH method is used to detect aneuploidy (para [0011], [0045], and [0117]), including aneuploidy of chromosomes 13, 18, 21, X and Y (para [0118]). Mohammed (Table 1) identifies a wide variety of disorders that are correlated with aneuploidy and which may thereby be diagnosed based on the findings of the disclosed array-based CGH method.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have performed the array-based CGH assay using binding agents that comprise polynucleotides complementary to each chromosome and using standards that are of a known karyotype, as taught by Mohammed, in order to have provided an effective method for determining the karyotype of a subject and thus any changes in the total number of chromosomes in a subject, which would thereby permit the diagnosis of a wide variety of disorders associated with chromosomal aneuploidy.

Regarding the recitation of “said microparticles for each chromosome are distinct in size and fluorescent intensity’ (claim 19, step (iii)), while Pinkel teaches that the binding agents are immobilized to microparticles that may be of different sizes, Pinkel

does not teach that the binding agents for different chromosomes are each immobilized to microparticles of different size and different fluorescent intensity.

However, the use of binding agents immobilized onto microparticles of different sizes and having different labels of different intensities was known in the art at the time the invention was made. In particular, Singh (page 6, lines 29-33; page 17, lines 5-17) teaches that microparticles of different sizes and different fluorescent emission intensity may be used together in combination to distinguish the binding of a target polynucleotide to one binding agent from the binding of another target polynucleotide to a different binding agent (page 11). It is stated that by using combinations of microparticles of different sizes and labeled with different fluorophores of different emission intensity, multiplex assays can be performed that allow for the simultaneous analysis of many different target nucleic acids (page 6, lines 29-33; and page 17). For instance, Singh teaches that a method that uses 10 different microparticles of different sizes, each labeled with one of 10 different fluorophores, will potentially provide 100 different microparticle populations. If each fluorophore is present at a different concentration, then 1,000 different populations of microparticles is possible, allowing for the use of 1,000 different probes in a single multiplex assay (page 17, lines 23-33).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have immobilized each binding agent specific to a different chromosome to microparticles of different sizes and labeled with different fluorescent labels of different emission intensity in order to have provided the advantage set forth by Singh of generating a multiplex

assay that could be used to simultaneously analyze for aneuploidy of multiple chromosomal targets.

Regarding claims 19-21, Pinkel teaches that the test/sample and reference/standard nucleic acids are obtained from a human (i.e., a diploid mammal; see col. 4, lines 16-20; col. 6, lines 31-41; col. 7, lines 36-41; and col. 13, lines 14-16).

Regarding claims 21, 23 and 24, Pinkel does not teach that the subject is an embryo; that said embryo is generated using *in vitro* fertilization; or that said aneuploidy is detected in said embryo prior to implantation of said embryo.

However, Mohammed teaches a method of detecting aneuploidy, wherein said subject is a mammal (page 2, paragraph 0015), said mammal is an embryo generated by *in vitro* fertilization (page 13, paragraph 0119), and said method results in preimplantation genetic diagnosis (i.e. detection of aneuploidy prior to implantation of said embryo) (page 13, paragraph 0119). Mohammed teaches that by analyzing embryos generated by *in vitro* fertilization prior to implantation of said embryo, abnormal embryos can be distinguished from normal embryos so that only normal embryos are used for implantation (para [0119]).

In view of the teachings of Mohammed, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the CGH method of Pinkel to the analysis of embryos generated by *in vitro* fertilization prior to implantation of said embryo, in order to have provided an effective means for identifying embryos with aneuploidy and thereby of providing a method that permitted the selection of embryos of normal ploidy for transplantation.

Regarding claim 27, Pinkel teaches that the binding agent (target) is a nucleic acid immobilized on a microparticle, and that the nucleic is complementary to and thereby has a binding specificity to the test/sample and reference/standard polynucleotides (column 4, lines 1-7, col. 4 lines 26-31 and col. 8, lines 57-61).

Regarding claim 28, Pinkel does not explicitly state that the microparticles are silica microparticles. However, Pinkel does separately teach immobilizing the binding agent onto microparticles and teaches that methods using arrays of small beads can achieve better sensitivity (col. 8, lines 57-65). Pinkel also teaches covalently attaching nucleic acid binding agents to silica (col. 9, lines 8-11). Pinkel states that fused silica provides a very low fluorescence substrate and a highly efficient hybridization environment (col. 9, lines 8-11) Further, Mohammed (para [0095]) teaches immobilizing nucleic acids onto a solid surface of fused silica. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have immobilized the binding agents onto silica microparticles, because silica provides a very low fluorescence substrate and a highly efficient hybridization environment. Therefore, it would have been prima facie obvious at the time the invention was made to used silica microparticles in the method of Pinkel for detecting aneuploidy, absent evidence to the contrary.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh, and further in view of Ibanez et al (Mol Reprod Dev. 2001 Feb;58(2):166-72).

The teachings of Pinkel, Mohammed and Singh are presented above.

Pinkel does not teach that the test/sample and reference/standard nucleic acids are from a subject that is a livestock animal, and particularly a livestock animal that is a cattle or sheep.

However, Mohammed teaches application of the CGH method to the detection of genetic mosaicism (defined therein as "the presence of two or more chromosomally distinct cell lines" [page 13, paragraph 0118], i.e. detection of aneuploidy between cell lines) in livestock (page 13, paragraph 0120). Mohammed teaches that genetic mosaicism is frequent in transgenic animals produced by pronuclear microinjection. It is stated that a successful method of screening for founder animals for germline mosaicism prior to mating would reduce costs associated with propagation of transgenic lines and improve the efficiency of transgenic livestock production.

Further, Ibanez teaches a method of detecting genetic mosaicism (pages 167-168) and teaches application of this method to the analysis of transgenic cattle and sheep founder animals (page 166, see introduction; page 171, see conclusion). It is stated that detection of mosaicism in livestock founder animals provides a more economic and faster alternative to breeding (see abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used test/sample and reference/standard nucleic acids obtained from livestock and particularly from cattle and sheep livestock, in order to have achieved the advantages disclosed by Mohammed and Ibanez of permitting the screening of cattle and sheep

livestock founder animals for germline mosaicism prior to mating, to thereby reduce the costs associated with the propagation of transgenic lines.

11. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh and further in view of Gvakharia et al (Fertility and Sterility. 2002 Sept; 78(Supplement 1):S229).

The teachings of Pinkel, Mohammed and Singh are presented above. Pinkel does not teach that the test/sample nucleic acids originate from an embryo.

However, as discussed above, Mohammed teaches performing the CGH analysis using an embryo to identify mosaicism in embryos prior to implantation. Mohammed states that the method is used for preimplantation genetic diagnosis. Further, Gvakharia teaches collecting cells from the blastomere stage to perform preimplantation genetic diagnosis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used test/sample nucleic acids that originated from a blastomere to detect aneuploidy in order to have provided a method that permitted the detection of aneuploidy in blastomeres prior to preimplantation of embryos derived therefrom, thereby facilitating the selection of embryos of normal ploidy for transplantation.

12. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh, and in further view of Bitner et al (US Patent Number 6,787,307).

The teachings of Pinkel, Mohammed and Singh are presented above.

Pinkel does not teach that the silica microparticles are silanized.

However, Mohammed (para [0098]) teaches that the solid surfaces to which the binding agent (probe) are immobilized may comprise a silane that provides a hydroxyl functional group for reaction with an amine group of the nucleic acid in order to facilitate the immobilization of nucleic acids.

Further, Bitner (abstract and col. 11, lines 53-60) teaches a method of detecting nucleic acid sequences in a sample using silica microparticles that are silanized and coupled to nucleic acids.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used silanized silica microparticles in order to have provided an effective means for immobilizing the nucleic acid binding agent to the microparticles.

Response to Remarks:

In the reply, Applicants traversed the previous rejections under 35 USC 103 over Pinkel et al.

Applicants state that claim 18 contains the limitation directed to the detection of aneuploidy in a subject. It is asserted that Pinkel teaches methods for detecting changes in copy number, such as deletions, duplications, inversions and translocations of segments of DNA and Pinkel does not teach detecting aneuploidy, which is indicative of "deletions or duplications of entire chromosomes, rather than merely segments of DNA along one or more chromosomes."

This argument has been fully considered but is not persuasive. As discussed in detail in the above rejection, the specification (page 26) states that aneuploidy may also include "partial monosomy conditions wherein a part of a chromosome is deleted" (emphasis added; page 26). Thereby, Applicants arguments are not consistent with the teachings in the specification because the specification does not limit the term aneuploidy to refer to deletions or duplications of entire chromosomes. In view of the teachings in the specification, the claims are considered to include methods which detect a change in copy number which is a deletion of a gene or a part of a chromosome. The method of Pinkel is considered to be one which detects “aneuploidy” as defined by the present specification. In particular, Pinkel states that “Variations in copy number detectable by the methods of the invention may arise in different ways. For example, copy number may be altered as a result of amplification or deletion of a chromosomal region. Alternatively, copy number may be reduced by genetic rearrangements that alter the sequences in the probe or target nucleic acids sufficient to reduce their binding” (col. 6, lines 55-63).

Further, to any extent that the claims as amended are intended to be directed to a method which detects a “deletion or duplication of an entire chromosome,” Pinkel does address the desire to detect such chromosomal abnormalities by stating that “perinatal genetic problems frequently result from loss or gain of chromosome segments such as trisomy 21 or the micro deletion syndromes. Thus, methods of prenatal detection of such abnormalities can be helpful in early diagnosis of disease” (col. 1, lines 28-32). Further, Mohammed has been cited for teaching the application of the

array-based CGH analysis method of Pinkel to the detection of a variation in the karyotype of a sample, and thereby the detection of aneuploidy (para [0004], [0012]). Mohammed specifically teaches that the array-based CGH method is used to detect aneuploidy (para [0011], [0045], and [0117]), including aneuploidy of chromosomes 13, 18, 21, X and Y (para [0118]). Mohammed (Table 1) identifies a wide variety of disorders that are correlated with aneuploidy and which may thereby diagnosed based on the findings of the disclosed array-based CGH method. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have performed the array-based CGH assay using binding agents that comprise polynucleotides complementary to each chromosome and using standards that are of a known karyotype, as taught by Mohammed, in order to have provided an effective method for determining the karyotype of a subject and thus any changes in the total number of chromosomes in a subject that would thereby permit the diagnosis of a wide variety of disorders associated with chromosomal aneuploidy.

Applicants assert that “Pinkel never mentions competitive binding and the conclusions in this reference are in no way based on the results of a competitive binding assay.”

This argument has been fully considered but is not persuasive. Comparative genomic hybridization (CGH), as taught by Pinkel, is a method well known to rely on competitive hybridization between the sample nucleic acid and the reference/control nucleic acid. Mohammed (para [0004]) clarifies this property of CGH stating that:

"The principle of the array CGH approach is simple. Equitable amounts of total genomic DNA from cells of a test sample and a reference sample (e.g., a sample from cells known to be free of chromosomal aberrations) are differentially labeled with fluorescent dyes and co-hybridized to the array of BACs, which contain the cloned genomic DNA fragments that collectively cover the cell's genome. The resulting co-hybridization produces a fluorescently labeled array, the coloration of which reflects the competitive hybridization of sequences in the test and reference genomic DNAs to the homologous sequences within the arrayed BACs" (emphasis added).

Further, Pinkel teaches that equal quantities of the sample and reference nucleic acids are mixed and contacted with the binding agent immobilized on the microparticle (see, e.g., col. 13). Pinkel also teaches that "Small array members containing small amounts of concentrated target DNA are conveniently used for high complexity comparative hybridizations since the total amount of probe available for binding to each element will be limited. Thus, it is advantageous to have small array members that contain a small amount of concentrated target DNA so that the signal that is obtained is highly localized and bright" (col. 8, line 61 to col. 9, line 1). Accordingly, Pinkel teaches that the CGH method requires the use of equal quantities of the test/sample and reference/standard nucleic acids and limited amounts of the binding agent and thereby the ordinary artisan would clearly recognize that the CGH method of Pinkel is a competitive binding assay.

Applicants state that "Pinkel's method would fail if it did not have an excess of immobilized binding agent because if the binding sites were saturated, or nearly

saturated, under one set of conditions, the method would not be able to detect an increase in copy number as no more target would bind and no more signal would be detected."

This argument has also been fully considered but is not persuasive. Applicants do not to provide any evidence to support their assertion that the method of Pinkel would fail if there was not an excess of immobilized binding agent. Further, this conclusion is contrary to the teachings of Pinkel which indicate that in fact a limiting amount of immobilized binding agent is used in the CGH method to effectively detect either an increase or decrease in copy number of chromosomal segments (see col. 8-9, cited above).

Applicants state that their method does not use reference probes and that the claimed method does not attempt to measure binding of reference probes to target elements. These arguments have been fully considered but are not persuasive. It is noted that the terminology used in the Pinkel patent is distinct from that used in the present application. However, the differences in terminology do not distinguish the claimed invention over that of Pinkel. The present claims use the terminology of "equivalent, non-aneuploid fluorescently-labeled polynucleotide standards." Pinkel uses the terminology of "reference probe" to refer to an identical nucleic acid that is obtained from normal/control cells that have two copies of each autosomal sequence and one or two copies of each sex chromosomal sequence – i.e. "non-aneuploid" (e.g., col. 3, lines21-34). Pinkel refers to the fluorescently-labeled nucleic acids obtained from the control sample that is non-aneuploid as a "probe." Again, the use of term "probe" as

opposed to “polynucleotide standards” does not distinguish the claimed invention over that of Pinkel. Accordingly, Applicant’s method and the method of Pinkel both include performing a step in which "reference probes" (fluorescently-labeled polynucleotides from a non-aneuploid sample) are contacted with the “target elements” (binding agents immobilized on the microparticles), and the binding of the reference probes to the target elements is quantified in order to determine the relative binding of the reference/standard probes as compared to the test/sample probes.

The response states that the “aforementioned deficiencies” are not taught or suggested by Mohammed et al or Singh et al. It is asserted that there would not be a reasonable expectation of success to overcome the “aforementioned pitfalls” by combining the methods of Pinkel and Mohammed and Singh. However, Applicants response does not specifically identify any pitfalls that would arise by combining the teachings of Pinkel, Mohammed and Singh. It is also argued that there would be no motivation to combine the teachings, Mohammed and Singh. This argument is contrary to the rejection which provides a clear statement of motivation for each modification of the method of Mohammed and Singh. The Singh reference specifically teaches the advantages of using microparticles having both different sizes and fluorescent intensities in order to permit the analysis of many different target chromosomal sequences simultaneously. Applicants provide no evidence or specific arguments as to why one would not have a reasonable expectation of success. As stated above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have immobilized each binding agent

specific to a different chromosome to microparticles of different sizes and labeled with different fluorescent labels of different emission intensity in order to have provided the advantage set forth by Singh of generating a multiplex assay that could be used to simultaneously analyze for aneuploidy of multiple chromosomal targets. Similarly, the motivation to combine the teachings of Pinkel and Mohammed are provided by the teachings of Mohammed reference wherein it is disclosed that the detection of a change in the number of chromosomes (i.e., karyotype) provides an effective means for diagnosing a wide variety of diseases known to be associated with the loss or gain of particular chromosomes.

The response asserts that the teachings of Ibanez, Gvakharia and Bitner do not cure the deficiencies of Pinkel and do not teach creating a detectable signal due to non-equal binding of a sample and the standard to microparticles. However, Ibanez was cited for its teachings of detecting genetic mosaicism in transgenic cattle and sheep founder animals; Gvakharia was cited for teaching analysis of cells from the blastomere stage to perform pre-implantation genetic diagnosis; and Bitner was cited for teaching detecting nucleic acid sequences in a sample using silica microparticles. Further, Pinkel does in fact teach a method of creating a detectable signal due to non-equal binding of a sample and a standard to microparticles, as discussed in detail above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634